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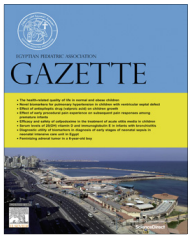

Efficacy and safety of cefpodoxime in the treatment of acute otitis media in children

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KEYWORDS

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Abstract *Background:* Acute otitis media (AOM) is a community-acquired respiratory tract infection in childhood frequently encountered by primary-care physicians and can cause a significant morbidity. Increasing bacterial resistance has led to concern about the current options for empirical antibiotic treatment and has prompted a search for effective treatments.
Objectives: To evaluate the clinical efficacy and safety of cefpodoxime proxetil in the treatment of children with acute otitis media.
Patients and methods: A prospective, multicenter study was conducted on 1380 children aged from 1 to 13 years with AOM who were prescribed a 5–10 day course of cefpodoxime proxetil (8 mg/kg/day). Patients were followed-up after 7–14 days from baseline visit. Efficacy was assessed by the percentage of patients with clinical cure, improvement or failure at the follow-up visit. Safety was evaluated by recording the occurrence and severity of any adverse events and by the physicians' and patients' assessment of overall tolerability.
Results: Clinically, 82.5% of patients were cured, 16.4% improved and there was failure of therapy in 1.1% of the patients. The overall combined cure and improvement rate of all related signs and symptoms was 98.9%. Adverse events, diarrhea and skin rash, were reported by only 16 patients (1.2%). The overall tolerability according to the physicians' and patients' assessment was excellent in 93.9% and 88.9%, respectively. Compliance was attained in 99.5% of patients.
Conclusion: Cefpodoxime proxetil is an effective, safe, well-tolerated antimicrobial agent for treatment of acute otitis media in children. It can be considered as an excellent choice for the empirical treatment of bacterial AOM.

Introduction

Acute otitis media (AOM) is one of the most frequent diseases in early infancy and childhood. It is defined as the presence of middle-ear effusion and a rapid onset of signs or symptoms of middle-ear inflammation, such as ear pain, otorrhea or fever.[1] It is estimated that more than two-thirds of children experience

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one or more attacks of AOM by the age of 3 years.[2–4] The peak age of incidence is 6–24 months and decreases with age.[5]

The pathogenesis of AOM is multifactorial, involving the adaptive and native immune system, Eustachian-tube dysfunction, viral and bacterial load, in addition to genetic and environmental factors.[2] Bacteria are believed to play a predominant role in the causation of AOM-related symptoms; therefore antibiotic therapy will accelerate the clinical recovery and may reduce the number of complications related to AOM.[4,6]

Streptococcus pneumoniae has been reported as the predominant pathogen causing AOM for many years, next to *Moraxella catarrhalis* and non-typeable *Haemophilus influenzae*. The implementation of vaccination programs for pneumococcal infection changed the etiology of AOM overtime resulting in *H. influenzae* to be the main pathogen in AOM.[7,8] Moreover, increasing bacterial resistance, particularly beta-lactamase producing strains of *H. influenzae* and *M. catarrhalis* as well as penicillin and macrolide resistance among *S. pneumoniae,* has raised the concern about the current options for empirical antibiotic treatment and has prompted a search for effective treatments.[1,6,9]

Cefpodoxime proxetil is an oral third generation cephalosporin of choice for the treatment of AOM.[1] It exhibits more balanced spectra of activity against the principal bacterial pathogens responsible for outpatient respiratory tract and other infections when compared with other widely used amoxicillin or oral cephalosporin of earlier generations.[10] *In vitro* studies show that it has activity against many common Gram-positive and Gram-negative pathogens associated with common pediatric infections including AOM, making it a useful option for empirical therapy.[1,6,11] Moreover, *in vivo* sensitivity studies assessing the bacteriological efficacy by examining middle-ear fluid before and a few days after the start of treatment and retrospective analyses of treatment failures, have shown a good bacteriological efficacy for cefpodoxime against *H. influenzae* and penicillin-susceptible *S. pneumoniae*.[7,8] It is highly stable to hydrolysis by the most commonly found plasmid-mediated β-lactamases.[10] As well, its concentration within the structures of the middle ear have been shown to achieve the minimum inhibitory concentration (MIC) for the microorganisms responsible for AOM with recommended dosing schedules. Its relatively long half-life and sustained tissue concentrations support twice daily dosing, representing an advantage over many other antibiotics with comparable clinical efficacy and features that may encourage patient compliance.[11]

Non-compliance is a common cause of treatment failure, clinicians should strongly consider factors that will enhance compliance, such as palatability, frequency of administration, adverse events (AEs) and cost. Finally, physicians' familiarity with dosing schedules and potential side effects may reduce prescribing errors.[12]

The aim of the study was to evaluate the clinical efficacy and safety of cefpodoxime proxetil in the treatment of children with acute otitis media.

Patients and methods

Study design

This prospective, multicenter study was conducted in 26 Egyptian medical centers, over a period of one year from January to December 2013. The study was approved by the local Ethics Committee. A written informed parental/guardians' consent was obtained prior to enrollment in the study.

Study population

A total of 1380 children aged 1–13 years, presenting with clinically diagnosed AOM suspected to be of bacterial origin were eligible for the study. Patients were not on any antibiotic therapy when enrolled in the study. The exclusion criteria were restricted to the contraindications to cefpodoxime given in the summary of the product characteristics, i.e. patients with known hypersensitivity to cephalosporin antibiotics.

Methods

Study procedure

The study was conducted in 2 visits, baseline visit at clinical evaluation and treatment initiation, and follow-up visit (day 7–14) following the routine practice of the trained physician.

Baseline visit

All candidates were subjected to comprehensive history-taking and clinical evaluation. The diagnosis of purulent AOM was based on a triad of recent clinical symptoms including otalgia, fever and irritability; tympanic membrane (TM) signs of AOM such as middle ear effusion characterized by bulging, limited or absent mobility of the TM or air-fluid level behind membrane; and otoscopic evidence of TM inflammation indicated by erythema, perforation or otorrhea in at least one ear were eligible for the study.[13] Patients fulfilling the eligibility criteria were prescribed cefpodoxime proxetil 8 mg/kg/day in two divided doses for 5–10 days. Additional medications for symptom relief were prescribed and documented.

Evaluation visit

The physician examined the patient and recorded their adherence to therapy, any drug adverse events and the clinical response to treatment. Symptoms of otalgia, fever and irritability were assessed and recorded. Otoscopy was performed to assess the tympanic membrane for severity of erythema, opacification, loss of light reflex, fullness or bulging, drainage, perforation, mobility and middle ear effusion. Patients were also monitored for any complications. Patients were considered to be compliant with the study medication if at least 80% of the antimicrobial course were taken according to the prescribed regimen; otherwise the patient was considered to be non-compliant.

Study endpoints

Primary and secondary endpoints were the efficacy and safety assessment of cefpodoxime, respectively.

Efficacy assessment

According to the physicians' assessment, efficacy was defined by the percentage of patients with either *clinical cure*: absence of fever, otalgia, irritability, and otoscopic signs of AOM; *clinical improvement*: clinical signs and symptoms including otoscopic findings diminished but did not completely resolve;

or *failure*: unsatisfactory resolution of tympanic membrane signs or symptoms of AOM, or worsening of the patients' condition.

Safety assessment

Safety was monitored by recording the cefpodoxime related-adverse events (AEs) during the observational period and by the physicians' and patients' assessment of overall tolerability at the end of the study. The recorded clinical AEs likely to be related to the use of antibiotics are vomiting, diarrhea or rash.[4,14] The severity was assessed by the physicians as mild, moderate or severe. Necessary treatment, outcome at time of report and serious criteria of AEs were recorded. The assessment of the overall tolerability was rated either: excellent, fair or poor.

Statistical analysis

Data were analyzed using Statistical Package for Social Sciences software version 17.0 (SPSS, Inc., Chicago, IL, USA). Numerical data were expressed as mean and standard deviation. Qualitative data were expressed as frequency and percentage. Chi-square test was used to examine the relation between the qualitative variables. p-value <0.05 was considered statistically significant.

Results

Two patients out of the enrolled 1380 patients did not show up at the follow-up visit and were excluded. Of the 1378 patients who completed the study, 788 (57.2%) were males and 590 (42.8%) were females, with a mean age of 3.8 ± 2.5 years. Their mean weight and length/height measured at the initial visit were 17.1 ± 7.1 kg and 94.4 ± 19.0 cm respectively.

At baseline visit

The mean temperature was 38.3 ± 0.7 °C. All children had one or more pretreatment AOM related signs and symptoms; the most frequent were otalgia (93.6%), spontaneous otorrhea (51%), purulent discharge (49.7%), fever (21.6%) and erythematous tympanic membrane (1.7%). In addition, nasal discharge was found in 3.3% of patients, sore throat in 2.4%, cough in 2.2%, and pharyngitis in 1.4% (Fig. 1). The onset of the first symptom occurred at less than 4 days prior to the baseline visit in 87.9% of the patients.

The most frequently reported prescription durations were five days in 783 (56.8%), seven days in 326 (23.7%) and ten days in 269 (19.5%) of the patients, with a mean duration of 6.5 ± 2.0 days. Other symptomatic medications were prescribed in 66.4% of the patients, including: antipyretics (24.7%), analgesics (22.1%), decongestants (14.6%), cough preparations (2.2%) and anti-inflammatory agents (8.3%).

At the follow-up visit

There was marked improvement of all AOM-related signs and symptoms. Seven patients (0.5%) were non-compliant. Among the remaining 1371 patients – according to physicians' assessment – 1131 patients (82.5%) were cured, 225 (16.4%) improved, and 15 (1.1%) failed to respond to therapy; with one reported worsening of patient's condition. Cure or improvement rate was 100% in all symptoms and signs except spontaneous otorrhea (98.0%), purulent discharge (98.5%) and nasal discharge (93.5%).

Patients that received a 5-day course of cefpodoxime had a significantly higher cure rate of 84.6% (659/779) compared to those taking cefpodoxime for a duration of more than 5 days (472/592, 79.7%) ($\chi^2 = 5.515$, $p = 0.019$).

Adverse events of cefpodoxime were reported by only 16 patients (1.2%), which included diarrhea ($n = 9$) and skin rash ($n = 7$). The nature of the AEs were mild to moderate and did not require any dose reduction or discontinuation of the prescribed course; while none of the AEs reported were serious and all resolved without sequelae (Table 1).

The overall tolerability of cefpodoxime according to the physicians' assessment was excellent in 1287 (93.9%) of patients, fair in 73 (5.3%) and poor in 11 (0.8%); while according to the patients' assessment, it was excellent in 1219 (88.9%), fair in 142 (10.4%) and poor in 10 (0.7%) (Fig. 2).

Discussion

Acute otitis media is a community-acquired respiratory tract infection, frequently encountered by primary-care physicians. Most often the bacterial etiology of infection is not confirmed prior to initiation of treatment, therefore physicians prescribing empirical antibiotics need to take into account the major causative bacteria.[1,6] The selection of the most effective antimicrobial to treat AOM has become more difficult in recent years because of increasing antibiotic resistance among all AOM pathogens to the standard first-line recommended antibiotics.[15,16] This has prompted a search for other safe, effective antibiotics necessary to achieve good clinical efficacy and help to prevent the development of resistance.[1,4,6,9] Empirical treatment by cephalosporin with beta lactamase stability should be preferred especially in cases with penicillin allergy. Cefpodoxime is one of three oral third generation cephalosporins recommended for empiric antibiotic treatment of AOM as designated by the AAP guidelines.[1]

The current multicenter study was designed to evaluate the efficacy and safety of cefpodoxime proxetil in the treatment of bacterial AOM in children. The patients were recruited from 26 centers located in different areas throughout Egypt covering various communities and socioeconomic classes. Thus, we believe that it can be a good representative sample of Egyptian pediatric population.

Findings of this study indicate that cefpodoxime is an effective antimicrobial agent for AOM. The 5–10 day treatment course resulted in an excellent response in signs and symptoms. Clinical cure was achieved in 82.5% of patients; and improvement in 16.4%, with an overall combined cure and improvement rate of 98.9%. The clinical efficacy of cefpodoxime in this study was found to be in line with earlier clinical studies for cefpodoxime who found that the overall combined cure and improvement rate ranged from 86% to 95%.[17–19] As well it is supported by the results of other earlier two trials concluding that cefpodoxime demonstrated significantly greater clinical efficacy and cure rates than either cefixime or amoxicil lin–clavulanate, respectively.[18,20]

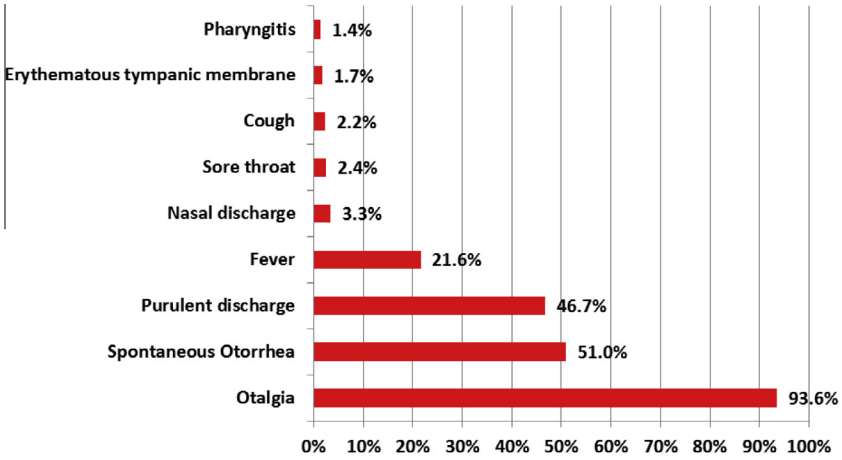

Figure 1 Signs and symptoms of acute otitis media at baseline visit (n = 1378).

Table 1 Cefpodoxime related-adverse events (n = 1371).

	Number	Percentage
Adverse event		
Diarrhea	9	0.7
Skin rash	7	0.5
Severity		
Mild	8	0.6
Moderate	8	0.6
Treatment		
No	8	0.6
Yes	8	0.6
Outcome at time of report		
Resolved	16	1.2
Serious criteria of adverse events		
No	16	1.2
Yes	0	0.0

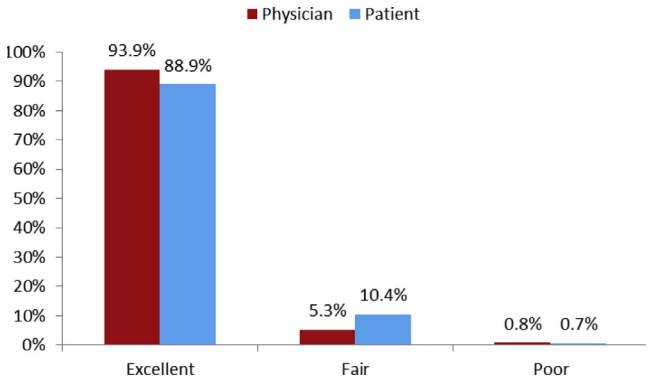

Figure 2 Tolerability assessment from the physicians' and patients' perspectives (n = 1371).

The optimal duration of antibiotic therapy for patients with AOM is uncertain.[1] In the present study it was found that cefpodoxime, in the 5-day treatment regimen, seems to be a suitable drug for AOM in children, with a significantly higher cure rate (84.6%) than an extended treatment course (79.7%) (p = 0.019).

Regarding safety, cefpodoxime was well tolerated by most patients. It has a tolerability profile similar to that of other oral cephalosporins, with gastrointestinal related symptoms and skin rash being the most frequently reported AEs.[21] The nature of the AEs were mild to moderate and did not require any dose reduction or discontinuation of the prescribed course; while none of the AEs reported were serious and all resolved without sequelae.

The twice daily regimen was acceptable to the majority of patients and accordingly compliance to treatment regimen was excellent (99.5%). It has been noted that patient compliance is inversely related to the frequency of drug administration and is directly related to the efficacy of the drug.[22] Moreover, the less frequent dosing schedule of cefpodoxime (bd) compared with either amoxicillin–clavulanate or cefaclor (tds), would be an added advantage for treatment with cefpodoxime.[21]

As a consequence, the efficacy and safety of cefpodoxime reported in this multicenter study is likely to be a true reflection of the effectiveness in actual clinical pediatric practice.

Conclusion

Cefpodoxime proxetil is an effective, safe, well-tolerated antimicrobial agent for treatment of acute otitis media in children. It is an excellent choice for the empirical treatment of bacterial AOM, with a recommended twice-daily regimen for an optimum duration of 5 days.

Specific contribution of each author to the study

1. *Mortada H. El-Shabrawi:* Contributed to the conception and design of the study; acquisition of data; drafting the article; approved the final version of manuscript to be published; and supervised the work.
2. *Omar A. Tolba:* Contributed to the analysis and interpretation of data; performed the statistical analysis and wrote the manuscript; reviewed the manuscript; and approved the final version of manuscript to be published.

3. *Tarek Z. El-Adly:* Contributed to the analysis and interpretation of data, drafting the article, revising the article, final approval of the version to be published.

Conflicts of interest

The authors declare no conflicts of interest.

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